Important Echocardiographic Parameters in Early Detection of Cardiac Involvement of Patients Suffering from Thalassemia Major

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Abstract

Background- Cardiac involvement is one of the most common causes of morbidity and mortality in patients with thalassemia major. In this study the echocardiographic parameters which would predict cardiac involvement in the patients at an early stage were determined.

Methods-A case control study was designed on 80 patients suffering from thalassemia major from September 2002 to December 2003 at a pediatric hospital. The following parameters were measured in the case group and age and sex-matched control group: isovolumic ventricular relaxation time (IVRT), deceleration time (DT), and pre-ejection period to ejection time (PEP/ET). Data were analyzed by T-student test and correlation coefficient.

Results- The mean age of the patients was 14.3±2.3 years, and age of the control group was 14±2.6 years. Mean ejection fraction in the case and control groups were 55.7±7.2 and 62.8±7.7 percent, respectively ($p<0.001$). Mean IVRT of the left ventricle was 126.21± 22.4 in the case group and 95.31±11.7 in the control group, ($p<0.05$). DT of the mitral valve in the case group was 144.67±23, in comparison to 141±30 ($p>0.05$) in the controls. Mean right ventricular IVRT in the case group was 128.18±21.62, and 98.32±15.16 ($p<0.05$) in the control group. Tricuspid valve DT in the case group was 134.87±25, and 144.93±20, ($p<0.05$) in the control group. PEP/ET in the left heart in the case group was 0.32±0.06, and 0.28±0.004 ($p<0.05$) in the control group. PEP/ET in the right side of the heart in the case group was 0.31±0.06 and in the control group, it was 0.26±0.04, ($p<0.05$).

Conclusion- The data show that IVRT in both ventricles regressed to the same extent, also decreased DT and increased PEP/ET in the right heart shows earlier right-sided failure ***(Iranian Heart Journal 2006; 7 (3):20-24)***.

Key words: thalassemia major ■cardiac involvement■ echocardiography

Thalassemia major is a severe and morbid hemolytic anemia that leads to growth disturbance, malfunction of different body organs and iron overload. In the past, the patients died before the first year of life, but now most of the thalassemic patients survive for more accurate diagnosis and treatment. Symptomatic treatment of thalassemia is expensive and leads to a high economic load on the government, especially in countries like Iran where the disease is epidemic.[1]

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The occurrence of beta gene in south and south-east of Iran is reported to be 8-10 percent. The genes of beta thalassemia are widespread and the disease is the most common genetic disorder in humans.[2] Cardiac symptoms and premature death due to cardiac involvement are still one of the greatest difficulties in management of these patients.[3] Iron overload due to frequent blood transfusion and intestinal uptake of iron lead to cardiomyopathy and is the major cause of morbidity and mortality in thalassemia major.[1] Iron is absorbed in ventricular myocardium and eventually in the conductive system of the heart.[2] The first manifestation of iron overload in the heart is pericarditis. The sequential manifestations are ventricular tachycardia, ventricular fibrillation and congestive heart failure.[4] Echocardiography can be utilized for assessment of iron overload in the heart and estimation of the result of chelator therapy.[5]

Methods

In this case-control study, all the eighty patients that were registered at the thalassemia ward of our center were included. The age of the patients was between 9-21 years and the study was performed from September 2002 to December 2003. First of all history and physical examination was performed for all the patients, followed by electrocardiography and chest radiograpy. In case of any arrhythmia or signs of cardiac enlargement on chest radiograph, the patients were excluded from the study. All patients underwent transfusions before echocardiography and after samples were sent for complete blood count and ferritin level, two dimensional, M-mode and Doppler echocardiography (Challenge 7000 with 2.5/3.5 and 3.5/5 MHz transducer) was performed by a pediatric cardiologist. In the study, also a control group at the same age and sex was assessed for diastolic function of the ventricles.

After physical examination and assurance of their health, echocardiography of the control group was performed by the same cardiologist. Echocardiography was performed with the patient in the supine position. M-mode was achieved at the tip of the mitral and tricuspid valves in the parasternal view. Left ventricular end-diastolic and end-systolic dimensions (LVEDD) (LVESD), ejection fraction (EF) and shortening fraction (SF) were measured by M-mode view. Pulsed Doppler was used to determine the blood flow through cardiac valves and parameters of E-velocity and A-velocity and pre-ejection period (PEP) and ejection time (ET) were measured. Then PEP/ET and E/A ratio were measured. Isovolumic relaxation time (IVRT) was measured with the probe at the apical five chamber view. Doppler view and M-mode were recorded on a paper with 50mm/sec velocity. Collected data were analyzed as mean ± standard deviation. Data analysis was performed by T-student test and correlation coefficient, and $p<0.05$ was considered as significant.

Results

Mean age of the patients was 14.3 ± 3.2 and 14 ± 2.6 in the control group. Mean heights of the patients and control group were 142.2 ± 12.3cm and 148.3±8.1cm, respectively. Mean weights were 34.5 ± 7.7 kg and 38.5 ± 7.7 kg. Mean body surface area of the patients was 1.16 ± 0.17 and 1.24 ± 0.23 square meters in the control group. Mean heart rate of the patients was 86.4±12.2bpm, and 81.7±12.3bpm in the control group, respectively. Mean ejection fraction of the patients was 55.7±7.2 and 62.8±7.7 in the control group, which was significantly decreased in the patients ($p<0.001$). Mean shortening fraction in the patients was 29.3±4.9 in comparison to the control group 34.07±6.1, and was significantly decreased ($p<0.001$, Table I).

Table I: Left ventricular volume, mass, cardiac mass index, cardiac index in patients with thalassemia major and controls

Variable	Patients	Control	P value
LA (cm)	3.11±0.44	2.6±0.29	<0.001
AO (cm)	2.26±0.32	2.22±0.24	NS
LA/AO	1.39±0.26	1.17±0.13	<0.001
CO (l/min)	6.619±1.8	5.8±1.6	<0.05
CI (l/min/m)	5.77±1.7	4.75±1.18	<0.05
LVMI(gr/m)	92.88±21.78	62.91±12	<0.05
SV (ml)	78.03±19.78	71.56±19.45	<0.05
LVEDD	4.8±0.6	4.6±0.4	<0.001
LVESD	3.4±0.5	3.1±0.4	<0.001
EF	55.7±7.2	62.8±7.7	<0.001
FS	29.3±4.9	34.07±6.1	<0.001

LA: Left atrium, AO: aorta, LA/AO: left atrial - aortic ratio, CO: cardiac output, CI: cardiac index, LVMI: left ventricular mass index, SV: stroke volume, LVEDD: left ventricular end diastolic dimension, LVESD: left ventricular end systolic dimension, EF: ejection fraction, FS: shortening fraction

Isovolumic relaxation time (IVRT) in the left ventricle was 126.21± 22.4 in the case group in comparison to the control group (95.31±11.7) that was increased significantly ($p<0.05$). Deceleration time of the mitral valve in the patient group was 144.67±23 in comparison to the control group (141.27±30, not significant, $p>0.05$). E/A ratio of the left ventricle in the patients was 1.81±0.35 in comparison to the control group's 1.72±0.45, and was increased significantly ($p<0.05$, Table II).

Table II: Left ventricular diastolic function in patients with beta thalassemia major and controls

Variable	Patients	Control	P value
Peak E(cm/s)	95.93(19.65)	89.66(20.2)	<0.05
Peak A(cm/s)	57.63(14)	57.10(15.7)	NS
E/A ratio	1.81(0.35)	1.72(0.45)	<0.05
DT (msec)	144.67(23)	141.27(30)	NS
IVRT(msec)	126.21(22.4)	95.31(11.7)	<0.05
PEP(msec)	0.089(0.014)	0.076(0.01)	<0.05
ET(msec)	0.28(0.03)	0.26(0.03)	<0.05
PEP/ET	0.32(0.06)	0.28(0.04)	<0.05

A: Early peak A velocity, E: Late peak E velocity, DT: Deceleration Time, IVRT: Isovolumic ventricular relaxation time, PEP: Pre – ejection period, ET:Ejection Time, PEP/ET: Pre-ejection time to ejection time ratio

IVRT of the right ventricle in the patients group was 128.18±21.62, and 98.32±15.16 in the controls, that was increased significantly in the patients ($p<0.05$) Deceleration time of the tricuspid valve was 134.87±25 in the patients and 144.93±20 in the controls, that showed significant decrease in the patients ($p<0.05$). E/A ratio of the right ventricle was 1.32±0.33 in patients and 1.21±0.23 in the control group, that was increased significantly ($p<0.05$, Table III).

Isovolumic relaxation time was increased in 54 patients (67.5%) in the left ventricle, and in 52 patients (65%) in the right ventricle. Tricuspid valve deceleration time was decreased in 40% and that of the mitral valve in 15 % of the patients. PEP/ET of the right side was 0.31± 0.06 in the patients and 0.26±0.04 in the control group, that was significantly increased in the patients ($p<0.05$).

Table III: Right ventricular diastolic function in patients with thalassemia major and controls

Variable	Patients	Control	P value
Peak E(cm/s)	61.6(13.5)	53.3(9.1)	<0.05
Peak A(cm/s)	48.05(11.5)	43.49(9.1)	<0.05
E/ARatio	1.32(0.33)	1.21(0.23)	<0.05
DT(msec)	134.87(25)	144.93(20)	<0.05
IVRT(msec)	128.18(21.62)	98.32(15.16)	<0.05
PEP(msec)	0.086(0.01)	0.079(0.09)	<0.05
ET(msec)	0.28(0.04)	0.27(002)	NS
PEP/ET	0.31(0.06)	0.28(0.04)	<0.05

A: Early peak A velocity, E: Late peak E velocity, DT: Deceleration time, IVRT: Isovolumic ventricular relaxation time, PEP: Pre–ejection period, ET: Ejection time, PEP/ET: Pre-ejection time to ejection time

Discussion

In patients suffering from thalassemia major, the height, weight and body surface area indices were significantly decreased. This difference was due to insufficient growth because of defective circulation. In this study, the diameter of the left atrium (LA) was increased but no change in the diameter of the aorta (AO) was observed. Nevertheless the LA/AO ratio was significantly increased in the patients in comparison to the control group. In a similar study by Agha and colleagues the result was similar.[6] In our study, like Bosi et al., the ejection fraction was decreased. 15 percent of the patients in our study had decreased ejection fraction, and shortening fraction was decreased in 20 (25%), that was due to left ventricular dysfunction. The stroke volume and cardiac index and cardiac output in our study were increased as in the study performed by Bosi and colleagues.[7] our study showed a significant increase in left ventricular mass index in the patient group. Agha and colleagues showed a similar increase in cardiac muscle mass in their study. Our study, as well as that of Agha[6] and Aldouri,[8] showed that the interventricular wall thickness was increased. Aldouri has shown that the heart of thalassemia patients was hypertrophied and was two times that of a normal heart. In our study as Akar study in 1994 LVEDD was increases in comparison to the LVESD.[9] Peak E velocity was increased in comparison to the LVESD.[9] Peak E velocity in thalassemia patients in comparison to the control group was increased significantly ($p<0.05$). Peak A in thalassemia patients and control group did not differ significantly. E/A ratio of the left ventricle in patients was increased in comparison to the control group ($p<0.05$), but E/A ratio was compromised only in 6.25% of the patients. Deceleration time in the mitral valve between the two groups did not differ significantly. Isovolumic relaxation time in patients was increased in comparison to the control group. The study showed abnormal left ventricular diastolic filling pattern due to hypertrophy and decreased compliance. Appleton has reported similar results.[10] Massuto and colleagues in 1994 have shown that increased E/A ratio and decreased IVRT and deceleration time as typical diastolic findings are due to restrictive cardiomyopathy. In this study nine patients (11.5%) had LVPEP/LVET more than 0.4, which was an indication of the left ventricular dysfunction. The maximum flow through tricuspid valve, peak E velocity in the patients in comparison to the control group was increased. Late peak velocity (A flow) of the tricuspid valve in patients in comparison to the control group was increased, but E/A ratio was disturbed significantly only in one patient (1.25%) Deceleration time of the tricuspid valve was decreased significantly in the patients in comparison to the control group. IVRT that shows diastolic dysfunction was increased in comparison to the control group. The study has shown an overall diastolic dysfunction of the right ventricle. In a study by Hahalis and colleagues, right ventricular filling pattern disorder in patients suffering from

thalassemia major was due to IVRT and in the left ventricle it was due to increased preload. Decreased deceleration time in the tricuspid valve can be utilized as good predictors of cardiac dysfunction.[12] These data are similar to our study. In this study increased PEP/ET ($p<0.05$) in thalassemia patients showed diastolic dysfunction of the right ventricle. Decreased deceleration time of tricuspid valve was seen in 32 patients (40%). It has been shown that 52 patients (65%) had increased IVRT in the right ventricle. The overall result of the study revealed a disturbed PEP/ET in the left ventricle in 11.5% and in the right ventricle in 50%. These data have both a prognostic and a diagnostic value. The isovolumic relaxation time in both ventricles was increased in a similar way. The above data show that serial echocardiography in patients with thalassemia major can help to detect cardiac involvement at an earlier stage.

References

1. Olivieri NF, Nathan DG, McMillan JH, et al. Survival of medically-treated patients with homozygous beta thalassemia. New Eng J Med1994; 331: 574-578.

2. Nathan DG, Oski FA. Hematology of Infancy and Childhood. 5th edition, 1999; p: 842-865.

3. Olivieri NF, Brittenham GM, Matusi D, et al. Iron chelation therapy with oral deforiprone in patients with thalassemia major. New Eng J Med 1995; 332: 918-22.

4. Ghafour AD, Gutgesell HP. Echocardiographic evaluation of left ventricular function in children with congestive cardiomyopathy. Am J Cardiol 1979; 44: 1332.

5. Henry W. Echocardiographic evaluation of the heart in thalassemia major Ann Intern Med1979; 91: 883.

6. Agha H, Mansour I. Echocardiographic features in patients with thalassemia major: evidence of abnormal relaxation pattern of the left ventricle. Egypt Heart Journal 49 (4): 475-481.

7. Bosi G, Crepaz MR,Gamberini Left ventricular remodeling and systolic and diastolic function in young adults with beta thalassemia major: a Doppler echocardiographic assessment and correlation with hematologic data. Heart 2003; 89: 762-766.

8. Aldouri MA, Wonk B, Hoffbrand AV, et al. High incidence of cardiomyopathy in beta thalassemia patients receiving regular transfusion and iron chelation: reversal by intensified chelation. Acta Hematol 84:113.

9. Kucuk N, Akar N. Evaluation of cardiac function in patients with thalassemia major Ann Nucl Med1999 Jun; 13(3):175-9.

10. Mossuto A Echocardiographic evaluation of the diastolic function in patients with beta thalassemia. Coure 1994;11/5: 437- 39.

11. Appleton CP, Hatle LK, Popp RL. Demonstration of restrictive ventricular physiology by Doppler echocardiography J Am Coll Cardiol 1988; 11: 757-68.

12. Hahalis G, Manolis AS, Gerasimidou I, et al. Right ventricular diastolic function in beta thalassemia major: echocardiography and clinical correlates Am Heart J 2001; March 141(3): 428-34.